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LETTER TO THE EDITOR

Cerebellar ataxia associated with anti-glutamic acid decarboxylase antibodies: a case report

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Dear Editor,

Anti-glutamic acid decarboxylase (GAD) autoantibodies have been first described in patients with diabetes mellitus type 1 (DM1) and then found to be associated with several neurological syndromes including cerebellar ataxia [1]. These antibodies are usually directed against the 65 kDa isoform of the enzyme glutamic acid decarboxylase (GAD65), which produces gamma-aminobutyric acid (GABA) from glutamate in the nerve terminals. In the cerebellum, anti-GAD antibodies impair the GABA-synthesis in the cerebellar basket and stellate cells leading to a reduced inhibitory GABAergic postsynaptic transmission from Purkinje cells [2].

Case report

A 39-year-old man from Cameroon was referred to our attention in January 2017 for a 3-year history of difficulties in fine movement and coordination on the right hand and leg, followed by postural and gait instability, dizziness, and nausea. He had no medical history and denied use of drugs, alcohol, or particular diet habits. Family history was negative for neurological problem. He had already performed computed tomography (CT) of the brain in 2011 [Fig. 1Aa] for an episode of severe headache and in 2014 [Fig. 1Ab] when also brain magnetic resonance imaging (MRI) [Fig. 1Ac] was performed after the onset of the main symptoms. At admission, neurological examination was relevant for downbeat nystagmus with torsional component in all gaze positions [Fig. 1b], right limb dysmetria and ataxic gait (International Cooperative Ataxia Rating Scale—ICARS: 16/100—subscore: posture-gait 7; kinetic functions 6; dysarthria 0; oculomotor 3). Routine blood analysis, including vitamin B12, vitamin E, glycated hemoglobin, and TSH levels was unremarkable. Anti-tissue transglutaminase and antigliadin IgG, ANA, ENA, and ANCA, onconeural antibodies (Hu, Ri, Yo, CV2, Amphiphysin, Ma2, and SOX1), and HIV 1–2 antibodies and VDRL were negative. Radioimmunoassay of anti-GAD65 antibodies was positive (titer > 2000 U/ml). Indirect immunofluorescence on a substrate of monkey cerebellum showed a pattern of immunoreactivity in the GABAergic terminals around Purkinje cells and on the granular layer [Fig. 1c]. Brain MRI [Fig. 1Ad] showed cortical atrophy of the right cerebellar hemisphere and right superior cerebellar peduncle without gadolinium enhancement. A lumbar puncture was performed and cerebral spinal fluid (CSF) analysis showed 19 WBC/uL (mononuclear cells 74%), total protein 74.6 mg/dL, and presence of several oligoclonal bands. Adenovirus, Ebstein Barr Virus, Varicella-Zoster Virus, Herpes Simplex Virus 1–2, Human Herpes Virus 6,

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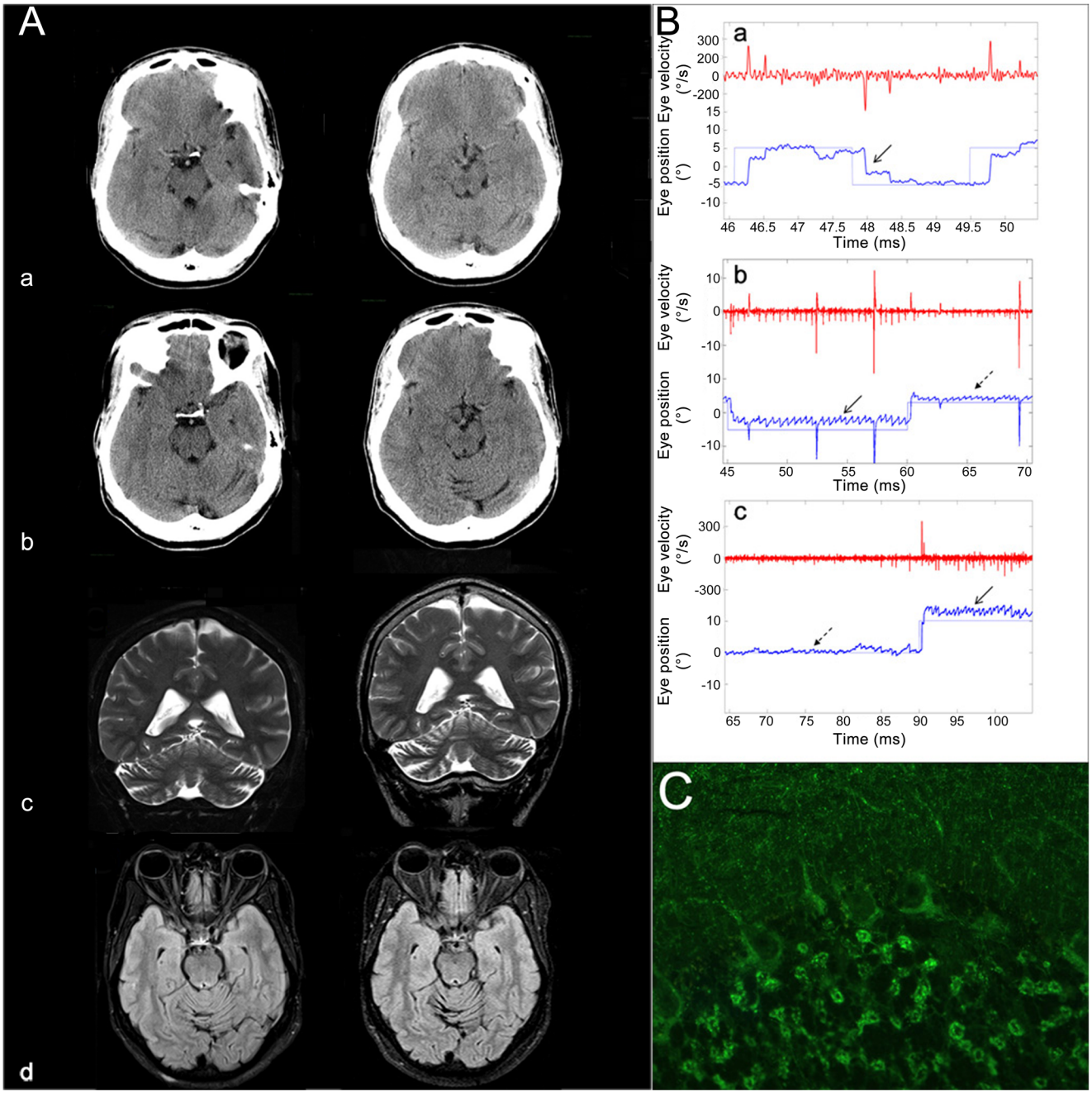

Fig. 1 (A) Neuroradiological work-up. Consecutive computed tomography axial scans obtained in January 2011 (a) and August 2014 (b), T2-weighted coronal and fluid-attenuated inversion-recovery axial magnetic resonance images obtained in August 2014 (c) and January 2017 (d) show clear-cut development of cerebellar hemispheres atrophy, mainly in the right side, with relative sparing of the vermis. (B) Eye-movement recording: horizontal saccadic eye movement recording; central eye position (0° amplitude) and rightward displacement (10°) are shown (a). Saccades are hypometric and followed by a corrective saccade both toward the eccentric position (dotted black arrow) and to the center (black arrow). Fixation task; on the downward gaze displacement (black arrow) and on central eye position (dotted black arrow), a downbeat nystagmus with mean frequency of 1.6 Hz is recorded (b). Fixation task; on the rightward gaze displacement, a gaze-evoked nystagmus with mean frequency of 2 Hz and quickphase to the right (black arrow) is recorded (c). In the central eye position, sporadic square wave jerks saccadic intrusions are present (dotted black arrow). (C) Indirect immunofluorescence of patient's serum on a substrate of monkey cerebellum: antibodies in patient's serum (1:20) detected with FITC-conjugated anti-IgAGM antibodies (Euroimmun) bound to GABAergic terminals around Purkinje cells and cerebellum granular layer.

Picornavirus, Borrelia burgdorferi, and Mycobacterium tuberculosis polymerase chain reaction (PCR) were negative. To exclude a possible paraneoplastic etiology, a total body CT and positron emission tomography (PET) scan were performed and resulted normal. Treatment was started with prednisone 1 mg/kg/day and stopped after 3 days because of

adverse effects; plasma exchange was performed for 6 days and then immunosuppressive treatment with azathioprine 2.5 mg/kg/day was started. Follow-up at 1 month showed worsening of the ataxic gait and dysmetria and new onset of dysarthria (ICARS: 42/100—subscore: posture-gait 20; kinetic functions 17; dysarthria 2; oculomotor 3), so intravenous immunoglobulin (IVIGs) 500 mg/kg/day were administered for 4 days. New follow-up at 3 months showed stability of the neurological conditions.

Discussion

The presence of anti-GAD antibodies have been associated with several neurological disorder: the most common is Stiff-Person syndrome (SPS), followed by cerebellar ataxia (CA), autoimmune encephalitis, and temporal lobe epilepsy [1]. Anti-GAD-associated CA is a rare disorder with prevalence of 1–2 cases per million. This condition is often associated with other autoimmune disorders and DM1 is the most common. In 12% of patients underlying neoplasia has been reported; small cell lung cancer, thymoma and breast cancer are the most common associated. In these cases, there is usually a lack of onconeural antibodies associated with the classical paraneoplastic CA, such as Purkinje cell cytoplasmic antibodies (anti-Yo) and antineuronal nuclear antibody type 1 (anti-Hu) [3]. Instead, it has been reported that in patients with different types of neurological syndromes and anti-GAD antibodies, the concurrent presence of anti-GABA-B receptor antibodies is only observed in the case of paraneoplastic syndrome [4]. Compared with classical paraneoplastic CA, patients with anti-GAD-associated CA and underlying neoplasia have a slower progression of disease and a better response to immunotherapy [3]. Unlike these tumor-associated conditions, our patient complained a rapid and severe progression of the cerebellar symptoms and signs with a very poor response to treatments.

Anti-GAD-associated CA is more common in women (80–90% of cases) and symptoms usually start in the fifth or sixth decade of life [2]. The most common manifestation is gait ataxia, followed by limb ataxia, dysarthria, nystagmus, and kinetic tremor [1]. Overlap with other neurological conditions associated with anti-GAD antibodies has been described, like muscular spasm and rigidity, drug-resistant focal epilepsy, opsoclonus-myoclonus syndrome, and Miller-Fisher syndrome [5]. Characteristic is downbeat nystagmus, which has been attributed to the impairment of inhibitory Purkinje cells of the floccular lobe, resulting in the disinhibition of the superior vestibular nucleus that project to the III cranial nerve nucleus. The resulted hyperactivity of neurons projecting to elevator eye muscles leads to upward eye deviation with corrective downward quick phases [5]. The diagnosis is made when high serum titer of anti-GAD antibodies is found in a patient with subacute or chronic cerebellar syndrome. The CSF analysis usually shows features of an immunological active process, like positive oligoclonal IgG bands and elevated intrathecal synthesis of anti-GAD antibodies. On brain MRI, cerebellar atrophy can be found [5]. In differential diagnosis, hereditary, degenerative, toxic, metabolic, other paraneoplastic, and autoimmune aetiologies of CA should be considered. There are no randomized controlled trial for treatment of anti-GAD-associated CA, but improvement with immunotherapy have been reported, with a better response in patients with subacute presentation. Generally, first line therapies include steroids and IVIGs, while if there is no improvement after 6 months of therapy, second line therapies, like rituximab, azathioprine and mycophenolate mofetil, should be considered [5].

In our case, the response to treatment was poor probably because the patient had a 3-year history of disease and cerebellar atrophy was already visible on brain MRI when the treatment was started. It is interesting to notice that cerebellar atrophy was asymmetric. This feature has been reported in other cases [6], being the atrophy localized in one or both cerebellar hemisphere or in vermis without uniform involvement of cerebellar cortex. The main pathogenic mechanism is the impairment in GABAergic transmission due to the reduction of presynaptic GABA production and neuronal loss with cerebellar atrophy in the advanced stage [2]. It has been speculated that other pathogenic mechanisms are involved in the neurodegenerative process such as the functional impairment of GABA-A receptors, which does not imply neuronal death [6]. Thus, different pathogenic pathways in different cerebellar area could explain the asymmetry of neuronal loss and thus atrophy.

In our patient, we did not find any other autoimmune disorder or cancer-associated disorder. However, a continuous surveillance is important for an early diagnosis of these associated conditions. In conclusion, anti-GAD-associated CA is a rare condition but it should be always considered in the case of non-genetic CA for response to treatment in early stages and the possible autoimmune and neoplastic diseases associated.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard The authors declare that the study has been performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki.

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